REMARKS

I. Introductory Comments

In the Final Office Action dated August 11, 2003, the Examiner indicated that the claims were rejected as follows: under 35 U.S.C. §102(e) as allegedly being anticipated by Bäckström *et al.* (U.S. Patent No. 5,952,008) (claims 1-5, 12-15, 17, 18 and 20-25); under 35 U.S.C. §103(a) as allegedly being unpatentable over Bäckström *et al.* (U.S. Patent No. 5,952,008) in view of Kamei *et al.* (U.S. Patent No. 5,575,987) (claims 6-11, 16 and 19); and under 35 U.S.C. §102(b) as allegedly being anticipated by Harai *et al.* (U.S. Patent No. 4,659,696) (claims 1-6, 11, 12, 16-22 and 25). The rejections are traversed for the reasons provided below.

II. Amendments to the Claims

Previously, claims 1-25 were pending. With the present amendment, Applicants seek to amend claims 1, 5, and 20 and cancel claim 13 without prejudice. Thus, claims 1-12 and 14-25 remain pending.

Support for the changes to the claims is identified below. Additional support other than that provided below may exist in the originally filed specification for one or more changes to the claims.

Claims 1 and 20 have been amended to delete the phrase "therapeutically effective amount." Support for powders comprising FSH in an amount other than a "therapeutically effective amount" is found in the section designated "Preparing the Compositions," which begins on page 10, line 10, of the originally filed specification. In addition, claims 1 and 20 have been amended to recite a powder comprising "a plurality of particles having a particle size of less than 10 microns MMD." Support for particles having a particle size in the stated range is found in the paragraph bridging pages 12 and 13 and in claim 13. Finally, claims 1 and 20 have been amended to correct a typographical error with respect to the word "penetration."

Claim 5 has been amended to delete cyclodextrin as a carbohydrate. Support for the carbohydrates remaining in the claim is found on page 9, lines 22-29.

As support for the claimed subject matter is found in the application as filed, no new matter is introduced by the entry of the above-identified changes to the claims. The changes to

the claims are made for clarification purposes only and should not be interpreted as acquiescence in any claim rejection.

III. The Rejection Under 35 U.S.C. §102(e)

The Examiner has maintained the rejection of claims 1-5, 12-15, 17, 18 and 20-25 under 35 U.S.C. §102(e) as allegedly being anticipated by Bäckström *et al.* (U.S. Patent No. 5,952,008). In their Reply of May 6, 2003, Applicants pointed out (among other things) that Bäckström *et al.* taught penetration enhancer-containing formulations while the pending claims recited formulations that are substantially free of any penetration enhancers. In response, the Examiner has taken the position that this difference is not sufficient to overcome the rejection. Specifically, the Examiner contends that Applicants' claims reciting a formulation substantially free of penetration enhancers does not exclude cyclodextrin, a substance described in Bäckström *et al.* as a penetration enhancer and in Applicants' specification as an excipient.

As stated in the Reply of May 6, 2003, the standard for anticipation is rigorous requiring that every element of the claimed invention be disclosed by a single prior art reference. *See Minnesota Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1565 (Fed.Cir.1992); *Scripps*, 927 F.2d at 1576-77; *Lindemann Maschinenfabrik GMBH, v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1458 (Fed.Cir.1984).

Responsive to the Examiner's concerns, then, Applicants have deleted "cyclodextrin" from claim 5. Furthermore, Applicants have reviewed all of the penetration enhancers (referred to as "enhancer compounds") described in Bäckström *et al.* to ensure that none of the specific penetration enhancers in the reference is recited in the claims. Thus, the subject matter of the amended claims is novel over the penetration enhancer-containing formulations described by Bäckström *et al.*

In view of the above, Applicants respectfully request reconsideration and removal of the rejection.

IV. The Rejection Under 35 U.S.C. §103(a)

The Examiner has maintained the rejection of claims 6-11, 16 and 19 under 35 U.S.C. §103(a) as being allegedly unpatentable over Bäckström *et al.* (U.S. Patent No. 5,952,008) in view of Kamei *et al.* (U.S. Patent No. 5,575,987). In their Reply of May 6, 2003, Applicants pointed

out (among other things) that there was no reasonable expectation of success should the cited references be combined given Bäckström *et al.*'s teaching of the criticality of enhancer compounds as a formulation component. The Examiner has nonetheless maintained the rejection.

This rejection is respectfully traversed in view of the following remarks.

The three basic criteria of *prima facie* case obviousness were outlined in the Reply of May 6, 2003. Applicants respectfully maintain that a *prima facie* case obviousness has not been made by the Examiner. Specifically, the requisite motivation to combine the cited references is lacking.

First, Bäckström *et al.*'s entire disclosure is premised on the finding that "when a peptide or protein ... is combined with an appropriate absorption enhancer and is introduced into the lung ... [, the peptide or protein] readily enters the pulmonary circulation by absorption through the layer of epithelial cells in the lower respiratory tract." See Bäckström *et al.* on page 1, lines 21-25. Thus, given the reference's emphasis on including an absorption enhancer in compositions intended for pulmonary delivery, Bäckström *et al.* can be viewed as *teaching away* from the present claims.

Furthermore, a careful reading of the reference reveals that the lowest amount of absorption enhancer taught by Bäckström *et al.* is about 10% relative to the polypeptide. See, for example, Bäckström *et al.* at page 4, line 16, which describes a ratio of polypeptide to enhancer from **about 9:1 to about 1:1**. Such ratios represent **10% to 50%** of the absorption enhancer relative to the polypeptide. In addition, each of the compositions provided in the Examples has a ratio of 9:1 or greater, which corresponds to an amount of the absorption enhancer of **10% or greater** relative to the polypeptide.

In contrast, Applicants recite compositions *substantially free* of penetration enhancers. Bäckström *et al.* -- a reference effectively teaching the requirement of including 10% or greater of an absorption enhancer -- in no way can be viewed as teaching formulations that are substantially free of penetration enhancers.

The Examiner alleges that Kamei *et al.* discloses compositions optionally comprising Tween 80, a compound exemplified in Applicants' specification as a penetration enhancer. In view of their disparate teachings, however, Bäckström *et al.* and Kamei *et al.* cannot reasonably be combined. Specifically, there is no reasonable basis to combine a reference (Bäckström *et al.*) advocating the use of absorption enhancers -- and at relatively high levels -- to enhance the flux of a protein through the epithelial layer with a reference (Kamei *et al.*) teaching that absorption

enhancers are optional or only used "where necessary." Thus, it is only by ignoring either Bäckström *et al.*'s teaching concerning the criticality of absorption enhancers or Kamei *et al.*'s teaching of certain absorption enhancers as merely an optional component that the cited references could be combined. In sum, there simply is no suggestion or motivation to combine these disparate references.

Assuming, *arguendo*, that such a motivation did exist, there is no motivation to modify the references' teachings in order to arrive at the claimed invention. For example, as pointed out above, one would first have to ignore Bäckström *et al.*'s teaching concerning the criticality of using an absorption enhancer. Even if one became convinced that absorption enhancers at levels below 10% would still provide sufficient absorption, there is no hint or suggestion to prepare formulations that are *substantially free* of absorption enhancers. Clearly, the suggestion to modify the references to reach the claimed invention comes only from the Examiner after reading the blueprint provided by Applicants' specification. This approach is consistently criticized as impermissible "hindsight reconstruction" and cannot be relied upon in the formation of a *prima facie* case of obviousness.

Thus, for all of the above reasons, the Examiner's *prima facie* case of obviousness with respect to claims 6-11, 16 and 19 is unsustainable. Consequently, reconsideration and withdrawal of the rejection is respectfully requested.

Although arguing for the nonobviousness of the independent claims over the cited art, Applicants, reserve the right to argue the nonobviousness of each and every rejected dependent claim. Applicants set forth the nonobviousness of the independent claims for expediency purposes only and it should not be construed as an acquiescence or admission that the subject matter of one or more dependent claims is obvious in view of the independent claim alleged to be obvious.

V. The Rejection Under 35 U.S.C. §102(a)

The Examiner has rejected claims 1-6, 11-12, 16-22 and 25 under 35 U.S.C. §102(a) as allegedly being anticipated by Hirai *et al.* (U.S. Patent No. 4,659,696). The Examiner has taken the position that Hirai *et al.* discloses each of the elements recited in claims 1-6, 11-12, 16-22 and 25 and 20-25.

The standard for anticipation has been set forth in Section III, *supra.*

Claims 1 and 20, the two pending independent claims, recite a powder formulation that comprises a plurality of particles having a particle size of less than 10 microns MMD. In

contrast, Hirai *et al.* discloses powdery compositions having particle sizes of about 20 to 250 microns. See column 4, lines 54-56. Because Hirai *et al.* does not teach compositions having particles in claimed range, the anticipation rejection cannot stand. Reconsideration and removal of the rejection under 35 U.S.C. 102(b) is respectfully requested.

VI. Conclusion

In view of the foregoing, Applicants submit that the pending claims satisfy the requirements of patentability and are therefore in condition for allowance. Reconsideration and withdrawal of all rejections is respectfully requested and a prompt mailing of a Notice of Allowance is earnestly solicited.

If a telephone conference would expedite the prosecution of the subject application, the Examiner is requested to call the undersigned at (650) 620-5506.

Respectfully submitted,
Inhale Therapeutic Systems, Inc.

Date: February 10, 2004

By: Mark A. Wilson
Mark A. Wilson
Registration No. 43,275

Nektar Therapeutics
150 Industrial Road
San Carlos, CA 94070
(650) 631-3100 (Telephone)
(650) 631-3125 (Facsimile)